CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

OXYDEMETON-METHYL
S-[2-(Ethylsulfinyl)ethyl] O,O-dimethyl phosphorothioate
Metasystox-R

SB 950-113 Tolerance # 330
Chemical Code: 382

Original date June 30, 1988
Revised: 8/16/88; 11/3/88; 6/19/89; 8/16/89; 10/12/89; 5/2/90
5/29/90; 5/13/91, 6/25/91 and 6/9/92, 9/1/95, 10/15/97

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect
Chronic toxicity, dog:	No data gap, no adverse effect
Oncogenicity, rat:	No data gap, no adverse effect
Oncogenicity, mouse:	No data gap, no adverse effect
Reproduction, rat:	No data gap, possible adverse effect
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, possible adverse effect
Chromosome effects:	No data gap, possible adverse effect
DNA damage:	No data gap, possible adverse effect
Neurotoxicity:	No data gap, no adverse effect

Toxicology one-liners are attached.

All record numbers for the above study types through 140416 (Document No. 205) were examined. This includes all relevant studies indexed by DPR as of October 15, 1997.

** indicates an acceptable study.
Bold face indicates a possible adverse effect.

File name: T971024
Revised by Name, Date: Revised by G. Chernoff, 5/2/90, J. Gee, 5/29/90, 5/13/91 and 6/9/92, P. Iyer, 9/1/95, J. Gee, 10/24/97

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may identify additional effects.

EPA Registration Standard, 9/87

Note: Some studies were conducted with approximately 50% oxydemeton-methyl in inert(s) and some with technical grade of >90%. At least aome of the studies analyzed for the content of a.i., so the doses are as noted. See 330-165, Record # 074208, page 5, for an explanation for the 50% oxydemeton methyl used in earlier studies. The more recent studies have used the actual technical grade of >90% purity. The inert diluent was added for long-term stability at room temperature but Mobay (via Dr. D. van Goethem) has had no problems conducting feeding studies with the real technical material. (Gee, 6/11/92).

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

COMBINED (CHRONIC/ONCOGENICITY) RAT

088, 151 008669, 072371, "Chronic feeding/oncogenicity study of oxydemeton- methyl (Metasystox-R) in Rats" (Mobay, 10/17/84). Metasystox-R 50% concentrate (50% oxydemeton-methyl in 4-methyl-2-pentenone) in the feed at 52, 4.6, 0.57, or 0 ppm AI (analytically-determined) to F344 rats (Charles River, MA), 50/sex/level, for 27 months; **NO ADVERSE EFFECTS - debilitated appearance from CHE inhibition >90% in high dose indicative of MTD; nominal ChE NOEL = 0.57 ppm; originally acceptable (Christopher 4/30/85) but unacceptable in second review: inadequate information and no eye exams. Martz 5/4/88, Davis 11/3/88. Record # 072371 contains appendices with clinical observations and data on animals which died before termination separated from those at terminal sacrifice. The study is upgraded to **ACCEPTABLE** status based on supplemental data for the rat and the negative eye exam in the dog study (#'s 008662, 074208). Gee, 5/31/89.
Note: EPA graded this study as "supplementary," with the "systemic, oncogenic NOEL = not determined (inadequate study report for assessment of chronic toxicity or oncogenic potential)." Davis, 1988. EPA evaluation of the study after submission of the appendices has not been available. Gee, 3/15/89.

117 051536, Exact duplicate of pages 68-109 in Record 8669.

150 072369, 072370, Supplement to 008669. Historical control data for tumor incidence Fischer 344 rats.

151 072371, Appendices for 008669 with data reformatted. Requested by EPA.

009 929662, Invalid IBT study. Not reviewed by Medical

CHRONIC TOXICITY, DOG

087, 165 008662, 074208, "R 2170 (C. N. Oxydemeton-methyl) Chronic Toxicity to Dogs on Oral Administration (12-Month Study by Gavage)", (Bayer AG, 6/7/84, and supplemental data, 6/15/88). Metasystox-R 50% concentrate (51.1% oxydemeton-methyl) at 1.25, 0.125, 0.0125, or 0 mg/kg/day a. i. in water to 6 beagles/sex/level for 1 year; initially reviewed as having **NO ADVERSE CHRONIC EFFECTS but unacceptable and no MTD, incomplete histopathology, no eye exams; only CHE inhibition of 40%. Christopher 5/1/85 and Martz 5/4/88. Record 074208 contains analyses of dosing solutions and explanation for the 50% concentration, stability data, individual histopathology and results of ophthalmological examinations, which apparently were done. Based upon the collective data and degree of cholinesterase inhibition, especially in the brain (46% at the high dose and 11% at the mid dose), the study is upgraded to **ACCEPTABLE** status with a ChE NOEL = 0.25 (0.125 oxydemeton-methyl) mg/kg/day. Gee, 5/31/89.
Note: EPA graded this study as "supplementary." but possibly upgradeable.

165 074208, Supplemental data for 008662. Addendum contains analyses of dosing solutions, clinical examinations, eye exams, individual pathology.

195 098152 Supplemental data for 008662. Mobay No.86797-2. Addendum containing statistical analyses of body weights, clinical chemistry, organ weights and hematology. No worksheet. No change in status of 008662. Gee, 6/9/92.

009 929663, Invalid IBT study. Not reviewed by Medical Toxicology.

ONCOGENICITY, MOUSE

** 199 119254, "Technical grade Oxydemeton-Methyl (Metasystox-R): An Oncogenicity feeding Study in the CD-1 Mouse" (W.R. Christenson and B.S. Wahle, Miles Inc., KS. Report # 103295, 11/2/1992). Technical grade oxydemeton-methyl with at least 91.6% purity was administered ad libitum in the diet for 21 months at 0 (1:1 acetone:corn oil mixed with Purina Mills Rodent Lab Chow 5001-4 in "etts" form), 3, 15 and 50 ppm to 50 CD-1 [Crl:CD-1(ICR)BR] mice/sex/group. Increased incidence of convulsions was noted in both sexes at 15 and 50 ppm and in controls at 9/50 in males and 5/50 in females. Histopathology revealed an increase in cytoplasmic vacuolation in the proximal body of the epididymes in males at 15 and 50 ppm levels. Adverse oncogenic effects are not indicated. Chronic NOEL = 3 ppm (epididymal vacuolation). Oncogenicity NOEL = 50 ppm. Cholinesterase NOEL = 3 ppm (Inhibition of plasma ChE 49%-88%; RBC ChE 25%-47% and Brain ChE 48%-73% at 15 and 50 ppm in both sexes). Acceptable. (H. Green and P. Iyer 9/1/95).

087, 158, 189 008663, 072598, 090714 "R 2170 (Metasystox R Active Ingredient; Oxydemeton-Methyl) Chronic Toxicity Study on Mice (Two-year Feeding Experiment)." (Kroerlinfer, F., E. Loeser and G. Kaliner, Bayer AG, Institute for Toxicology, Wuppertal, FRG; Mobay Nos. 69986, 69986-1 and 69986-2, 7/2/81 for initial report) Oxydemeton-methyl, "technical grade" at 93.7 and 91.4% was fed in the diet at 100, 30, 10, or 0 ppm AI to CF-1 mice with 70/sex/level for 2 years. Ten/sex/group were sacrificed at 12 months. Initially reviewed as having no adverse effects but unacceptable and not upgradeable with insufficient information for assessment due to substantial deficiencies including lack of feed analysis and incomplete histopathology. Christopher 5/1/85 and Martz 5/4/88. Record 072598 contains analyses of the diet, individual data for the limited list of tissues examined, tables of incidences separated into

terminal sacrifice and moribund/dead animals. The study remained unacceptable and not upgradeable. Gee, 5/31/89. Document 330-189, Record 090714 was submitted as the final version of 072598. Rereview of all submissions confirms that the study is **UNACCEPTABLE AND NOT UPGRADEABLE** based on major deficiencies of inadequate diet analyses, inadequate histopathology and histopathology data presentation, husbandry problems with excessive autolysis of animals. Gee, 5/25/90.
Note: EPA did not grade this study due to major deficiencies.

REPRODUCTION, RAT

104 038280 "R2170 (c.n. Oxydemeton-methyl) Two-generation Study with Rats", (Bayer. AG, Inst. Toxicol.,9/26/85, Report No. 90584). Oxydemeton-methyl, 52.5% with remainder methylisobutylketone, in the feed to 10/sex/level Wistar rats (Winkelmann) at 50, 10, 1, or 0 ppm (AI or bulk?) with 2 litters/generation; **ADVERSE EFFECTS** - epididymal epithelial vacuolization and testicular atrophy/aspermia, NOEL = 1 ppm; decreased fertility, litter size, postnatal survival and growth, overall NOEL = 1 ppm; actual NOEL lower due to rapid degradation in feed; **UNACCEPTABLE** and not upgradeable: cannot verify intended exposures. Martz 12/27/85.
Note: EPA originally graded this study as "supplementary" due to reporting deficiencies.

096 019988, Interim report for 038280.

034 929668-70, "Metasystox. -R, three generation rat breeding studies", (Harris Labs, 5/27/66). Metasystox-R (grade?) at 50, 25, 10, or 0 ppm in the feed to 10 males/level and 20 females/level; **ADVERSE EFFECTS**: reduced fertility, litter size, and pup survival at 50 ppm, histological evidence of "depressed oogenesis" at 50 and 25 ppm; cross-breeding experiment in F3b showed fertility reduction in 50 ppm males mated with control females equivalent to that in control males mated with 50 ppm females, therefore not male or female specific. **UNACCEPTABLE** and not upgradeable due to multiple deficiencies. Christopher, 4/30/85 and Martz, 5/4/88.
EPA One-liner: REASSESSMENT (6/6/84). Levels tested: 0, 10, 25, 50 ppm. Reproductive NOEL = 10 ppm. Reproductive LEL = 25 ppm. Histological effect on oogenesis. RBC ChE NOEL = undetermined. RBC ChE LEL = 10 ppm. 67% and 61% of control (F3b female pups and parents). CORE Grade Supplementary due to incomplete litter data, no clinical sign or mortality data for dams, no individual animal data, inadequate identification of test compound purity.

134 060990, "Male reproductive toxicity study in rats with oxydemeton-methyl (Metasystox-R) in the diet", (D. A. Eigenberg, Mobay, 12/28/87, Study No. 86-671-01, Report 94986). Metasystox-R, 50% concentrate (50% oxydemeton-methyl) in the feed at 50, 9, 3, or 0 ppm to male CD rats (Charles River, MI), 40/sex/level with sacrifice of 9-10/sex/level at 2, 4, 6, or 8 months, with recovery groups at 50 ppm, 4-10/group, treated/withdrawn for 3.5/0.5, 4/2, 6/3, and 6/4 months; **ADVERSE EFFECT**: epididymal epithelial vacuolation in 50 and 9 ppm groups at 2-8 months, nearly complete recovery in 6/4 withdrawal group; no effects on testicular weights and morphology, or on sperm count, motility, or morphology. **SUPPLEMENTAL STUDY**, not graded. Martz 5/5/88.

134 060990, (Appendix to above): "A two month reproductive toxicity study in rats with oxydemeton-methyl [Metasystox-R] (50% concentrate and technical grade) and methyl isobutyl ketone in the diet", (Mobay, 12/28/87). Metasystox-R 50% concentrate ("MSR", 50%

oxydemeton-methyl), oxydemeton-methyl ("ODM", 95% pure), or methyl isobutyl ketone ("MIBK", 99%) in the feed at 50 ppm AI or control feed to male CD rats (Charles River, MI) for 1 or 2 months with recovery groups treated/withdrawn for 2/1 and 2/2 months; **ADVERSE EFFECT**: epididymal epithelial vacuolation in ODM groups, nearly complete recovery in 2/2 month ODM and MSR groups, no effect in MIBK group; no effects on testicular weights and morphology, or on sperm count,
motility, or morphology. **SUPPLEMENTAL STUDY**, not graded. Martz 5/5/88.

119 054350 and 124 057658, 057662, Supplemental to 060990: protocol for satellite study (Male Reproductive Toxicity in Rats with Metasystox-R in the Diet), with letter to Mobay dated 11/10/86 concerning CDFA's comments on protocol, and reply from Mobay dated 12/5/86 (Martz 3/4/88, Chernoff, 5/1/90).

124 057660, Supplemental to 060990: homogeneity and stability analyses; diet preparation protocol.

120 054689, 122 057656, 124 057661, 126 060211, Supplemental to 060990: two, four, and six months progress reports.

110 054141 "Analytical Chemistry Report. The Evaporation of Methyl Isobutyl Ketone (MIBK) from Rodent Ration Stored in Rat Feeders". (Mobay, 2/10/86 (report 710)) MIBK at 100 ppm in feed had 4.5 hour half-life at room temperature, with 96% evaporated in 24 hours. MIBK constitutes one-half of METASYSTOX-R 50% concentrate, added to stabilize oxydemeton-methyl. Martz 3/4/88.

194 096808 "Male Reproductive Toxicity Study in Rats with Oxydemeton Methyl (Metasystox-R) in the Diet." (D. A. Eigenberg and R. F. Hastings, Mobay Corporation, Stilwell, KS, 12/28/87, No. 94986-1) See reviews and one-liners of 060990 in 330-134 for details of study conduct. This supplement presents the results of nine rats fed 50 ppm MSR for 8 months followed by 5 months on the control diet. Sperm motility, morphology and count, and testicular weights showed no effects but there were no concurrent controls. Comparisons were made to earlier results. Two of the nine had minimal vacuolation of the epididymides, stated to be indistinguishable from aging changes. No adverse effect is flagged for this portion of the study. Gee, 5/13/91.

154 072521, "Male Reproductive Effects of Metasystox-R (MSR) After Short Term Exposure", (Microbiological Associates, Mobay study 98462, 1/27/89). Metasystox-R (oxydemeton-methyl) technical, 92%, lot 87R0010M; given by oral gavage to male Crl:CD (SD) BR rats for 5 consecutive days, at doses of 0 (water), 0.15, 0.9 or 5.0 mg/kg, 20/dose for breeding and 15 per dose for testicular evaluation by sacrifice on days 1, 7, 14, 21, 35, 56 and 112 after dosing period; no cholinesterase measurement; breeders were mated for 5 days with 1 female per male for seven mating periods; there was no apparent effect on the data from the seven matings but no positive control included for dominant lethal portion of study; in the males for testicular evaluation, body weight loss occurred during dosing at 5.0 mg/kg/day with subsequent recovery over time to control levels; percent sperm motility was reduced in the high dose group at day 1 and 7 sacrifice and in the mid- (62.5%) and high-dose (60.2%) groups at week 35 compared with controls (72.5%); in the pathology portion, the only finding noted was at day 116 at 5.0 mg/kg with 13/15 showing epithelial vacuolization in the corpus epididymis compared to 5/15 in the controls, 8/15 at 0.15 and 6/15 at 0.9 mg/kg but no significant finding in the caput or cauda

epididymis; **SUPPLEMENTAL STUDY**. Gee, 3/8/89. 330-194, 096807 contains the registrant's responses to questions raised by the reviewer, Dr. Anderson of EPA. The comments of EPA were mainly asking for clarification of methods. No change in status. Gee, 5/10/91.

174 074927, "Position Paper on the Reproductive Toxicity of Oxydemeton-Methyl (METASYSTOX-R)", (Eigenberg, D.A., Mobay Corporation, Toxicology Dept., Stilwell, KS., 8/16/89). Summary of results and response to EPA comments, with the conclusion that oxydemeton-methyl has reproductive effects only at highly toxic doses after subchronic exposure. No worksheet provided (G. Chernoff, 5/1/90).

194 096809 "Evaluation of Sperm Motility in Rats Treated with Oxydemeton Methyl for One, Two, and Three Months in the Diet Using the National Toxicology Program Method." (D. A. Eigenberg, Mobay Corporation, Stilwell, KS, No. 100594, 2/14/91) Oxydemeton methyl, technical grade, 91.6 - 93.6% purity, was fed in the diet at 0, 3, 9 or 50 ppm to 40 male CD Sprague-Dawley rats. Ten per group were sacrificed at 0, 1, 2 or 3 months. Sperm motility (collected from the distal cauda) was determined using a procedure based on the protocol of the National Toxicology Program in which the microscope stage is preheated to 37^{o} while scoring. In addition, the buffer contained egg yolk rather than bovine albumin. There were no differences in sperm motility between treatment and control groups. RBC, plasma and brain cholinesterase activities were inhibited in a dose-dependent relationship although no cholinergic signs were reported. No effect on the testes was reported. The only effect noted as a **possible adverse effect** is the vacuolization of the epididymal tubular epithelium at 50 ppm (30/30) and 9 ppm (4/30). No findings are reported for the controls and 3 ppm groups. This is the same effect noted in other studies. **Supplemental study.** Gee, 5/14/91.

174 074928, "Male Reproductive Toxicity Study in Rats with Oxydemeton-Methyl (METASYSTOX-R) in the Diet - Electron Microscopy of the Epididymis", (Mueller, R.E., Mobay Corporation, Toxicology Dept., Stilwell, KS., Study #86-671-01, 8/16/89). This is a very brief report, with 8 micrographs, in which it is concluded that the morphologic changes seen in the epididymal cells are compatible with a physiologic response to stimulation or increased functional demand presumably related to oxydemeton-methyl-induced cholinesterase inhibition. No worksheet provided. (G. Chernoff, 5/1/90)

****188 090538**, "Two-Generation Dietary Reproduction Study in Rats Using Oxydemeton-Methyl (METASYSTOX-R), Report No. 100029", (D.A. Eigenberg, Mobay Corp., Toxicology Dept., Study No. 87-671-01/87-671-02, March 30, 1990). Oxydemeton-Methyl (ODM) technical, 94.6%, batch PT 808-406-113 was diluted with Methyl Isobutyl Ketone Technical (MIKT), 99.1%, batch 87R001M, to formulate ODM concentrate, 50%. Seven groups of 35 male and female CD Sprague-Dawley rats each, were administered diets containing 50% ODM at doses of 0 (corn oil control), 1, 3, 9, and 50 ppm, technical ODM at 50 ppm, or MIKT at 50 ppm, for two generations, two litters/generation. Effects reported at 50 ppm 50% and technical ODM were increased epididymal vacuolation and decreased fertility, gestational weight gain, litter size, day 4 and 21 pup viability, pup weaning weight, maternal ovarian weight, and corpora lutea number. Brain cholinesterase levels were significantly depressed at 1 ppm, but no overt clinical manifestations were reported at any dose tested. No treatment related effects were seen with 50 ppm MIKT. Nominal Reproductive NOEL = 9 ppm (decreased fertility and litter size, altered ovarian and epididymal histology); Nominal Developmental NOEL = 9 ppm (decreased viability and postnatal growth retardation based on body weight); Nominal Cholinesterase NOEL < 1 ppm (statistical

decrease); Nominal Cholinesterase NOAEL > 50 ppm (no overt clinical manifestations). The study is **ACCEPTABLE**, and a **POSSIBLE ADVERSE REPRODUCTIVE HEALTH EFFECT** (altered ovarian and epididymal histology, and decreased fertility), and a **POSSIBLE ADVERSE DEVELOPMENTAL HEALTH EFFECT** (decreased pup viability) are noted (G. Chernoff, 5/1/90).

124 057663, Supplemental to 090538: protocols.

SUMMARY: The table below summarizes the findings from the 4 multigeneration studies examining the reproductive effects of ODM in rats. In spite of the fact that the studies were conducted at different times, in different laboratories, using different strains of rats, the results are amazingly consistent. Decreases in fertility, litter size, and viability were reported in each of the three studies where 50% ODM was administered to both females and males. Associated with these findings was epididymal vacuolation, which was also observed in the study where treatment was restricted to males. An additional finding was an alteration in ovarian histology, described in one study as evidence of "depressed oogenesis", and in another as a decrease in the number of corpora lutea. Taken together, these studies suggest a treatment-related increase in epididymal and ovarian histopathology which is associated with decreased fertility and litter size. The finding from a cross breeding experiment (record no. 929668-70), in which fertility was reduced equally regardless of the sex treated, supports the notion that the primary lesion involves gonadal histology of both sexes. NOEL's for these studies ranged from 1 to 9 ppm, with LOAEL's ranging from 9 to 50 ppm. Using the findings from the acceptable study (record no. 090538), the NOEL is 9 ppm. As in the studies with 50% ODM, studies with the technical grade of ODM (94.6%) showed adverse effects on gonadal histology, fertility, and litter size. In contrast, studies with methyl isobutyl ketone technical (MIKT), the diluent used in formulating 50% ODM, failed to demonstrate these effects. Taken together, these findings indicate that it is the ODM, and not the MIKT diluent, that is responsible for the observed adverse effects. The argument has been presented that the adverse reproductive effects occur only at doses which are near the upper limits compatible with life (record no. 074928, pg. 9). This argument is apparently based upon the observation of decreased maternal weight gain during gestation, and decreased plasma, rbc, and brain cholinesterase levels. The fact that the decreased gestational weight gain was associated with decreased litter size, and that overt clinical signs (salivation, tremors, seizures, or deaths) associated with cholinesterase inhibition were absent, raises serious doubts about the validity of the argument. In the absence of more convincing evidence, the adverse reproductive and developmental effects are considered treatment related and not the result of extreme parental toxicity near the upper limits compatible with life (G. Chernoff, 5/1/90). Since this summary was written, two additional supplemental studies have been reviewed - 096808 and 096809 in 330-194. Record 096808 supports the recovery from vacuolization of the epithelium of the epididymides with time after cessation of treatment. (Gee, 5/14/91)

Study No.	038280	929668	090538	060990	060990	090538
% ODM	52.5	(?)	50	50	94.6	94.6
ppm	1,10,50	10,25,50	1,3,9,50	3,9,50	50	50
sex treated	m&f	m&f	m&f	m	m	m&f
NOEL (ppm)	1	10	9	3	<50	<50
LOAEL (ppm)	10	25	50	9	50	50
vacuolation	+	?*	+	+	+	+
dec. fertility	+	+	+	nm**	nm	+
dec. litter size	+	+	+	nm	nm	+
dec. viability	+	+	+	nm	nm	+
ovarian abn.	?*	+	+	nm	nm	+

* ? = no mention of this variable in the CDFA one-liner.
** nm = this variable was not measured in the study.

Note: In preparation of the risk assessment document, the toxicologists thought the NOEL of 3 ppm from Record No. 060990, Mobay 98-671-01, 1987, for epididymal effects should be used. Although the study was not acceptable for SB950 purposes - and was not designed to be - the findings are of sufficient quality to use. (Gee, 6/25/91)

198 119189, "A Male Fertility Study in Rats Using Technical Grade Oxydemeton Methyl Administered Via the Diet, (D. A. Eigenberg and T. F. Hastings, Miles, Inc., KS., Report Numbers 103251 and 103251-1, 27 July 1992). This study was conducted to determine if vacuolation of the corpus epididymis and fertility reduction observed in previous rat reproduction studies at 50 ppm, could be correlated. Technical grade oxydemeton methyl with 92.5% indicated purity was administered in the diet to 40 CD Sprague-Dawley male rats per group at concentrations of 0 (Purina Rodent Laboratory Chow 5001-4 Etts form) and 50 ppm for 10 weeks prior to mating with untreated females. 23 females in control group and 27 females in the 50 ppm group had 12.5. and 12.1 mean fetuses/female respectively. Micropathology revealed vacuolation of the epididymides in 0/40 at 0 ppm and 40/40 males at 50 ppm. Fertility was evaluated by examining the number of implantation sites, number of fetuses per litter and number of litters from untreated females mated to exposed males. **Supplemental** to record numbers 38280 and 90538. (H.Green and P.Iyer 7/7/95).

REPRODUCTION, CHICKEN

009 929667, "Meta-Systox-R. Three Generation Breeding Study on Poultry", (Harris Laboratories, 5/24/66). Metasystox-R (99.5%) at 0, 10, 50, and 100 ppm to groups of 4 male and 20 female Leghorn chickens each generation; **INSUFFICIENT INFORMATION FOR ASSESSMENT; UNACCEPTABLE**: multiple protocol and technical deficiencies. Christopher 4/22/85.
EPA One-liner: ChE NOEL < 10 ppm (lowest level tested). Reproductive NOEL = 100 ppm. Systemic NOEL = 100 ppm (highest level tested). Dosage Levels = 10, 50, and 100 ppm.

TERATOLOGY, RAT

089 008655, "Evaluation for Embryotoxic and Teratogenic Effects in Orally Dosed Rats", (Bayer AG, 6/8/79, #8436). Oxydemeton-methyl (93.5%) by oral gavage at 0, 0.3, 1.0, and 3.0 mg/kg/day for 10 days (6 - 15 of gestation) to 22, 20, 20, and 21 Long Evans FB 30 female rats, respectively, in Experiment 1 and at 0 and 3.0 mg/kg/day for 10 days to 25 female rats in Experiment 2; **POSSIBLE ADVERSE EFFECT**-Teratogenicity (telencephalic hypoplasia) NOEL = 1.0 mg/kg/day; Fetotoxicity (stunted fetuses) NOEL = 1.0 mg/kg/day; Maternal toxicity-Females at 3.0 mg/kg/day showed decreased weight gain in Experiment 1 but not Experiment 2; **UNACCEPTABLE-**may not have achieved MTD, no dosing solution analysis, use of 50% concentrate. Christopher 4/26/85.
EPA one-liner: Study inadequate for determination of NOEL. Data suggestive of positive response. More data requested from registrant in order to evaluate this study. CORE Grade Supplementary.
NOTE: This one-liner predates the following submission.

071 000049, Supplementary information as requested by EPA (cover letter dated 5/10/84), including photocopies of figures from the report; copies of the standard operating procedures for skeletal examinations; individual dam body weight data; and Caesarean section, soft tissue, and skeletal staining results; data sheets for the second phase of the study; historical control data. No worksheet done. Davis 6/20/88.

069 022755, "Frequency of Stunted Fetuses in Control Groups from Embryotoxicity Experiments on Bay: FB 30 Rats". Data from 30 control groups from consecutive experiments between August, 1978 and May, 1981 on the frequencies of stunted fetuses. No worksheet done. Davis 6/21/88.

069 001375, "Compilation of the 'Spontaneous Malformations' in the Rat Strain FB 30 (Long Evans) from 1971 - 1980". Data from 30 control groups from consecutive experiments between August 1978 and May 1981, on the array and frequencies of spontaneous malformations. No worksheet done. Christopher 4/25/85, Davis 6/21/88.

096 019989, "A Teratology Study in the Rat with Metasystox-R", (Miles Laboratories, 2/13/85). Metasystox-R (90.6%) by oral gavage at 0, 0.5, 1.5, and 4.5 mg/kg/day for 10 days (6 - 15 of gestation) to 45 inseminated Charles River COBS CD females per group; sacrifices in each group - 5 on day 16, 28 on day 20, 12 on day 21 postpartum; **NO ADVERSE EFFECT-No evidence of developmental toxicity, refuting the Bayer AG study results (Record 8655); maternal toxicity NOEL = 1.5 mg/kg/day (tremors, decreased weight gain, cholinesterase inhibition); **ACCEPTABLE**. Christopher 4/30/85, Martz 2/10/88.

086 008658, Proposed protocol for Record 19989. Reviewed by Medical Toxicology-see Knaak letter of 10/9/84.

096 019990, Final protocol 8454 for Record 19989.

096 019991, Summary of Range Finding Study for Record 19989 (Appendix K).

096 019992, Data from neurobehavioral testing for Record 19989 (Appendix K).

092 026387-91, Developmental/behavioral testing protocols for Miles Laboratories reproduction studies.

109 043563, "Response to EPA Comments on Metasystox-R Rat Teratology Study", (Miles, 2/13/86). Data include individual clinical observations, fetal body weights, developmental indices and test results of neonatal behavior. Gee, 6/19/89.

COMMENT: Both CDFA and EPA found the results of the Bayer AG study (Record 008655) suggestive of a positive effect in developmental toxicity. However, both agencies have found these findings to be adequately refuted in the Miles Laboratories study (Record 019989), particularly since the study is acceptable. Therefore, the data gap is filled and there is no adverse effect. Davis, 6/88.

TERATOLOGY, RABBIT

** 330- 089 008654, 172 075497, 201 125076 "A Teratology Study in the Rabbit with Metasystox-R"; Miles Laboratories, Inc., 4/10/84, #86391; Metasystox-R (50% concentrate in methyl isobutyl ketone = 53.5% active ingredient) at 0, 0.1, 0.4, and 1.6 mg/kg/day by gavage for 13 days (7 - 19 of gestation) to 17 American Dutch female rabbits/group; **NO ADVERSE EFFECT** - Neither developmental nor systemic maternal NOEL established - NOAEL's $\geq$ 1.6 mg/kg/day; Maternal NOEL of 0.4 mg/kg/day (actual active ingredient of 0.2 mg/kg/day) for cholinesterase inhibition. Initially reviewed as unacceptable (failed to achieve MTD, ambiguous chemistry data) Christopher 4/26/85. Study considered possibly upgradeable with justification of dose selection. Gee, 5/31/89. Record # 075497 contains data on the individual body weights in the range-finding study at 0.1, 0.5, 1, 3, 6 and 12 mg/kg. Upgraded to **ACCEPTABLE** (Gee, 8/15/89). Supplemental information (Record # 125076) providing the skeletal evaluation of 20 litters previously thought to be disarticulated and hence not evaluated were examined and results submitted. Also data previously evaluated with the fetus as the unit were evaluated with the litter as the unit. No treatment-related effects were noted in the skeletal system of the litters examined (Iyer, P 9/1/95).

EPA One-liner: Teratogenic NOEL > 0.8 mg/kg (HDT). Fetotoxic NOEL < 0.05 mg/kg (very minor effect of incomplete ossification of the metacarpals-no further studies requested). Maternal ChE NOEL = 0.20 mg/kg/day. Maternal ChE LEL = 0.80 mg/kg/day (20% decrease in brain ChE and 45% decrease in RBC ChE). Levels tested by gavage in American Dutch strain - 0, 0.1, 0.4, 1.6 mg/kg of a 50% material (0.05, 0.2, 0.8 mg/kg of active ingredient).

093 019979, Most complete version of Record 8654, including individual fetal weights. No separate worksheet. Christopher 4/26/85.

070 008635, Pages 311 - 333 of rabbit teratology study (Record 8654).

093 020056, Supplementary study which attempts by cholinesterase results to validate the dose levels used in the main study. Does were dosed by gavage at the same dose levels as the main study on days 7 - 19; enzyme reductions at day 20 in the high dose group were 20.7% for brain and 43.3% for erythrocytes; at day 28, the reductions were 22.1% for brain and 29.8% for

erythrocytes; plasma levels were not reduced at either day. In the absence of maternal toxicity or corroborative evidence of sufficient CHE inhibition, the dose levels in the main study are judged to be too low. No worksheet done. Christopher 4/25/85, Martz 1988. See comment under 008654 above. Gee, 5/31/89.

146 (no record number), Mobay Corporation rebuttal argues that an MTD was reached, based on previously evaluated material. No change in status resulted. Davis 11/3/88. At a meeting held March 15, 1989 with CDFA, the sponsor again discussed the dose selection and presented data from a pilot study in which 1/3 aborted and 3/3 had weight loss - amount not given - at 3.0 mg/kg (50% active ingredient). No cholinesterase data included. EPA has accepted the study in question. Gee, 3/15/89.

009 929666, Invalid IBT study. Not reviewed by Medical Toxicology.

GENE MUTATION

****089 008638**, "Mutagenicity Evaluation of R2170, C.N. Oxydemeton-methyl, in the Mouse Lymphoma Forward Mutation Assay", (Litton (Netherlands), 3/84). Oxydemeton-methyl, "93.7%/96.1%" pure, at 1500, 1250, 1000, 750, 500, 100, or 0 nl/ml (solvent control) without S9 and EMS positive control, or 50, 25, 10, 2, or 0 (solvent control) nl/ml with S9 and 3-MC positive control, in L5178Y TK+/- cell line; $\geq$ 1250 nl/ml > 90% cytotoxic without S9, $\leq$ 50 nl/ml with activation, probably a confounding factor; **ADVERSE EFFECT**, dose-dependent increase in mutant frequencies (> 2x control). **ACCEPTABLE**. Christopher 4/25/85, Martz 3/8/88.

089 008652, "R 2170 - Salmonella/microsome Test for Detection of Point-mutagenic Effects", (Bayer, 1/16/80). Oxydemeton-methyl, 92.2% pure, with strains TA1535, TA1537, TA98, and TA100 with and without Aroclor-induced male Sprague-Dawley rat S9, at 12500 to 20 ug/plate plus negative and positive (endoxan or trypaflavin) controls; **ADVERSE EFFECT**, increased revertants (>2x control) in TA1535, LEL=500 ug/plate (equivocal) -S9 and 2500 ug/plate +S9, in TA100, LEL=6000 ug/plate -S9 and 12000 ug/plate +S9, no response in TA1537 or TA98. **UNACCEPTABLE,** individual plate counts not given. Christopher 4/23/85, Martz 8/19/88.

089 008645, (see also 8645 under Chromosome Mutation-sister chromatid exchange and micronucleus)**:** "Mutagenic Studies on the Insecticide Metasystox-R with Different Genetic Systems", (Indian Institute of Science (India), Mutation Research, 124:97-102, 1983). Metasystox-R (commercially-obtained; no AI content given), in Salmonella strains TA98 and 100, $\pm$ S9 (source?), at 500, 100, 50, 10, or 0 ug (AI or bulk?)/plate, with 50 ug/plate NTG (?) positive control; **ADVERSE EFFECTS**, revertants 60X or 4X above control with TA98 or TA100, respectively, at 50 ug/plate, with growth inhibition $\geq$ 100 ug/plate, NOEL=10 ug/plate; **UNACCEPTABLE** in absence of individual data. See 39106 and 39107 for other tests in same report. Christopher 4/25/85, Martz 3/8/88.

089 008649, (see also 8649 under DNA Damage/Repair): "Mutagenicity Evaluation of R 2170 in the Rec Assay and the Reverse Mutation Induction Assay", (Litton, 4/80). "R 2170," AI content unspecified, at 5000, 2500, 1000, 500, 100, 10, 1, 0.5 or 0 ug/plate in Saccharomyces cerevisiae strains S138 or S211C $\pm$ Aroclor induced male Sprague Dawley rat S9, with quinicrine mustard, ethylmethane sulfonate, or 2-anthramine (ANTH) as positive controls; **NO ADVERSE EFFECTS**, cytotoxicity +S9 at 2500 and 5000 ug, poor response with ANTH +S9;

UNACCEPTABLE and not upgradeable - test article composition not identified, single platings with no replicate test, and failure of positive control. Christopher 4/24/85, Martz 3/4/88.

089 008653, "Mutagenicity of Organophosphorus Compounds in Bacteria and Drosophila", (Monash Univ., Australia, Mutation Research, 28:405-420, 1975). 140 OP's, including demeton-S-methyl ("METASYSTOX-i"), demeton-S-methyl sulphone, and demeton-S-methyl sulfoxide (oxydemeton-methyl), were tested in E. coli, Salmonella typhimurium, and Drosophila, with no activation systems, and no dose levels or plate counts identified; **ADVERSE EFFECTS**, **positive responses noted in E. coli strain WP2uvrA with oxydemeton-methyl** and WP2uvrA and WP67 with the sulphone; in Salmonella strains TA 1530 and 1535 and E. coli strain WP2uvrA and Drosophila with demeton-S-methyl. **UNACCEPTABLE** in the absence of details. Christopher 4/23/85, Martz 3/4/88.

089 008640, "5-Methyltryptophan Resistance Mutations in Escherichia coli K-12. Mutagenic Activity of Monofunctional Alkylating Agents including Organophosphorus Insecticides", (Laboratory for Mutagenicity Testing of the German Federal Government, Mutation Research, 20:7-15, 1973). Oxydemeton-methyl, no purity or source, with beta-propiolactone, N-methyl-N'-nitro-nitrosoguanidine (MNNG), and methyl methanesulfonate (MMS) positive controls; **ADVERSE EFFECTS**, oxydemeton-methyl, 1 mM (LDT), was mutagenic, potency order: MNNG >MMS >dichlorvos >oxydemeton-methyl >dimethoate >bidrin, with methylparathion "probably mutagenic" and malathion, parathion and diazinon negative. **UNACCEPTABLE** for data requirement but with useful information. Christopher 4/22/85, Martz 3/8/88.

**** 330-197 112215** "R 2170 Spot Test on Cross-Bred C57Bl/6J x T Stock Mouse Fetuses to Evaluate for Induced Somatic Changes in the Genes of the Coat Pigment Cells." (Herbold, B.A., Bayer AG Department of Toxicology, Mobay No. 101927, 10/9/91) R2170 (oxydemeton-methyl), approximately 92-93 %, was given in a single oral dose on day "10" of gestation to female C57Bl/6J mice in two trials. Doses on the first were 0 (water), 5, 10 and 20 mg/kg b wt. In the second trial doses were 0, 12, 16 and 20 mg/kg. Sufficient mice were dosed (number not given) to provide for more than 300 F1 animals for examination. The F1 were examined for the "relevant spots" (RS) on days 12-16 and again on days
25-35. In addition, "white mid-ventral spots" (WMVS) were also scored. Ethylnitrosourea wa the positive control. At 20 mg/kg, mortality occurred with 8/178 in trial 1 and 6/150 in trial 2 dying from acute effects. Clinical signs were seen at 16 and 20 mg/kg (described but no data included). Possible adverse effect of in vivo genotoxicity with an increase in relevant spots at 20 mg/kg. Acceptable. Gee, 6/9/92.

COMMENT: The gene mutation category is satisfied by the acceptable mouse lymphoma assay (Record 008638). This assay demonstrated mutagenicity, as did four of the other five studies (evaluated as unacceptable). It is also noted that mutagenicity was found with and without activation, which is also true for the chromosome mutation studies. Davis, 7/1/88. An additional study (Record # 112215) with a possible adverse effect in vivo has been reviewed. Gee 6/9/92.

CHROMOSOME EFFECTS

136 065425, "Clastogenic Evaluation of R 2170 in an In Vitro Cytogenetic Assay Measuring Chromosome Aberration Frequencies in Chinese Hamster Ovary (CHO) Cells", (Hazleton Biotechnologies Veenendaal Laboratory, 9/1/87, Mobay Report # 95604). Chinese hamster

ovary cells were exposed to Metasystox-R (95.2 - 95.5% pure, batch 808506108) at 1.0, 1.5, 2.0, 2.5 mg/ml for 7.5 hours (low dose) or 17.7 hours (other doses) without activation and 2.0, 3.0, 4.0, 5.0 mg/ml for 2 hours with activation; **ACCEPTABLE; POSSIBLE ADVERSE EFFECT**-The frequencies of chromosome aberrations were elevated in a dose related fashion both with and without activation. Davis 6/23/88.

****140 068455**, "Chromosome Aberrations in Chinese Hamster Ovary (CHO) Cells", (Microbiological Associates, Inc., Study No. T5572.337, 2/29/88). Chinese hamster ovary cells were exposed to Metasystox-R (94.6% pure, Lot No. Pt 808406113) at 0, 0.13, 0.25, 0.5, 1 ul/ml for 14 hours without activation and 0.6, 1.3, 2.5, 5 ul/ml for 2 hours with activation; **ACCEPTABLE; POSSIBLE ADVERSE EFFECT**-The frequencies of chromosome aberrations were elevated both with and without activation. Davis 6/29/88.

****140 068454**, "Sister Chromatid Exchange Assay in Chinese Hamster Ovary (CHO) Cells", (Microbiological Associates, Inc., Study No. T5572.334, 2/29/88). Chinese hamster ovary cells were exposed to Metasystox-R (94.6% pure, Lot No. Pt 808406113) at 0, 0.08, 0.16, 0.3, 0.6 ul/ml for 25 hours without activation and 0, 0.6, 1.3, 2.5, 5 ul/ml for 2 hours with activation; **ACCEPTABLE; POSSIBLE ADVERSE EFFECT**-Sister chromatid exchange frequencies were significantly elevated ($p < 0.01$) at all dose levels both with and without a ctivation; this was dose-related in the presence of activation. Davis 6/29/88.

143 064891, "Dominant Lethal Mutations in Mice. Final Report", (Mobay Report # 94974, Microbiological Associates, 12/15/87). Metasystox-R 12chnical, 92.2% pure, batch 87R0010M, at 0, 0.9, 1.75, or 3.5 mg/kg once by IP injection to 20 CD-1 males/level; mated with 2 virgin females/male every 7 days, starting with day of treatment, for total of 8 matings; **ACCEPTABLE; NO MUTAGENICITY - No effect on fertility index, total implants, dead implants, or live implants; minimal clinical signs**.** Davis 8/15/88

139 067956, "Dominant Lethal Mutations in Mice. Final Report.", (Microbiological Associates, 3/2/88, Mobay Report # 94974-1). Metasystox-R Technical, 92.2% pure, batch 87R0010M, at 4.25 or 0 mg/kg once by IP injection to 20 CD-1 males/level, mated with 2 virgin females/male every 7 days, starting with day of treatment, for total of 8 matings; **NO MUTAGENICITY**-No effect on fertility index, total implantations, dead implantations, or live implantations; minimal clinical signs; **SUPPLEMENTAL STUDY.** Davis 6/23/88.

089, 013 008651 "R 2170 - Dominant Lethal Study on Male Mouse to Test for Mutagenic Effects", (Bayer, 1/16/80). Oxydemeton-methyl, 92.2% pure, at 5 or 0 mg/kg once by oral gavage in 0.5% Cremaphor to 50 NMRI (Ivanovas GmbH) males/level, mated with 50 NMRI females/group every 4 days, starting with day of treatment, for total of 12 matings; **NO EFFECTS** on pregnancy index, preimplantation losses, or postimplantation losses, or clinical signs; **UNACCEPTABLE**: no positive control and single dose level with no evidence of an MTD. Christopher 4/24/85, Martz 3/8/88.
EPA One-liner: NOEL > 5 mg/kg (only level tested).

089 008643, "Studies on the Cytogenetic Effects of Oxydemeton-methyl in the Human Leukocyte and Mouse Micronucleus Test Systems", (Maharashtra Assoc. for the Cultivation of Sci. (India), short communication in Mutation Research, 78:385-387, 1980). Oxydemeton-methyl ("technical grade" from Bayer): (1) in human lymphocytes at "final concentration" of 1 mM to 1 nM, with 100 metaphases examined/level, and (2) in "young Swiss male mice," 3/level, i.p. at 3,

2, 1, or 0 mg/kg/day x 2 days, with 1000 PCE's/mouse; **ADVERSE EFFECTS:** (1) aberrations as chromatid and isochromatid breaks, dose-related, 0.05 to 0.21 breaks/cell in 5% to 17% of cells, no NOEL, and (2) dose-related increase in average number of micronucleated cells, 7.0 to 10.3 vs 2.7 in control, no NOEL. **UNACCEPTABLE**, no positive controls and no individual information. Christopher 4/23/85, Martz 3/8/88.

089 008647, "R 2170, Oxydemeton-Methyl, METASYSTOX-R active ingredient, Sister Chromatid Exchange in the Bone Marrow of the Chinese Hamster In Vivo to Test for Potential DNA Damage", (Bayer, 10/4/83). Oxydemeton-methyl, 94.4% pure, at 6, 3, or 0 mg/kg, with endoxan (cyclophosphamide?) as positive control, in water once i.p., to Chinese hamsters (in-house bred), 5/sex/level; **NO ADVERSE EFFECT,** NO SCE's; **UNACCEPTABLE** and not upgradeable - insufficient high dose. Christopher 4/25/85, Martz 3/4/88

089 008639, "Sister Chromatid Exchanges in Chinese Hamster Cells Treated with Seventeen Organophosphorus Compounds in the Presence of a Metabolic Activation system", (Roswell Park, Environmental Mutagenesis, 4:621-24, 1982). Oxydemeton-methyl, no source or purity, in V79 cells +S9 at 80, 40, 20, 10, 0 ug/ml with cyclophosphamide as positive control, 5 ug/ml: **ADVERSE EFFECT**, increased SCE/cell, 8.3 or 7.3 at 80 or 40 ug/ml vs 6.1 in control or 21.0 in positive control, NOEL=20 ug/ml. **UNACCEPTABLE** for data requirement but has useful information. See 8637 for similar study done without S9. Christopher 4/24/85, Martz 3/8/88.

089 008637, "Sister-Chromatid Exchanges and Cell-cycle Delay in Chinese Hamster V79 cells Treated with 9 Organophosphorus Compounds (8 Pesticides and 1 Defoliant", (Roswell Park, Mutation Research, 103:307-313, 1982). Oxydemeton-methyl, 97.5% from Mobay, in V79 cells 80, 40, 20, or 0 ug/ml in DMSO, without activation, 100 metaphases/level; **ADVERSE EFFECT**, increased SCE/cell at 80 ug/ml, 10.5 vs 6.8 in DMSO control, NOEL=40 ug/ml. **UNACCEPTABLE** for data requirement but has useful information. See 8639 for similar study done with S9. Christopher 4/24/85, Martz 3/8/88.

089 008645, (see also 8645 in the following one-liner and under Gene Mutation): "Mutagenic Studies on the Insecticide Metasystox-R with Different Genetic Systems", (Indian Institute of Science (India), Mutation Research, 124:97-102, 1983). Metasystox-R (commercially-obtained; no AI content given), sister-chromatid exchange, "healthy male donor" lymphocytes with 120, 80, 40, 20, 10, 5, or 0 ug/ml; **ADVERSE EFFECT,** significant dose-related increase of SCE's/metaphase, NOEL = 10 ug/ml, growth inhibition at 120 ug/ml; **UNACCEPTABLE** in the absence of individual data. Christopher 4/25/85, Martz 3/8/88 (no new Worksheet).

089 008645, (see also 8645 in the preceding one-liner and under Gene Mutation) "Mutagenic Studies on the Insecticide Metasystox-R with Different Genetic Systems", (Indian Institute of Science (India), Mutation Research, 124:97-102, 1983). Metasystox-R (commercially-obtained; no AI content given), in mouse ("Swiss albino") bone marrow micronucleus test, 18 (claimed MTD), 15, 10, or 5 mg/kg/day to 6/level with vehicle to 3, sex unspecified, i.p. x 2 days with kill 6 hours after second dose, mitomycin C at 5 mg/kg/day as positive control, 1800 PCE's/smear; **ADVERSE EFFECT**, significant dose-related positive response but cytotoxic at all positive doses, NOEL = 5 mg/kg/day; **UNACCEPTABLE** protocol and no individual data. Christopher 4/25/85, Martz 3/8/88 (no new Worksheet).

089 008650, "R 2170 - Metasystox R Active Ingredient - oxydemeton-methyl Methyl - Demeton-S-methylsulfoxide - Micronucleus Test on Mouse to Evaluate R 2170 for Mutagenic

Potential", (Bayer, 6/27/80). Oxydemeton-methyl, 92.2% pure, by oral gavage, at 5, 2.5, or 0 mg/kg/day x 2 days in 0.5% Cremaphor, or trenimon (?) at 0.25 mg/kg x 2 days as positive control, to 5/sex/level NMRI mice (Ivanovas GmbH), with marrow harvest 6 hours after second dose, 1000 PCE's/mouse counted; **NO ADVERSE EFFECT**, no clinical signs; **UNACCEPTABLE** - inappropriate sampling times. Christopher 4/24/85, Martz 3/3/88.

089 008648, "R 2170 - Demeton-S-methylsulfoxide - Oxydemeton-Methyl -Metasystox R Active Ingredient - Micronucleus Test on Mouse to Evaluate R 2170 for Mutagenic Potential", (Bayer, 6/30/81). Oxydemeton-methyl, 94.7% pure, by **i.p. injection** at 6, 3 or 0 mg/kg/day x 2 days in peanut oil; trenimon, 0.25 mg/kg in water x 2 days as positive control; 5/sex/level NMRI mice (Winkelmann), with marrow harvest 6 hours after second dose; 1000 PCE's/mouse counted; **NO ADVERSE EFFECT**, no clinical signs; **UNACCEPTABLE** - inappropriate sampling times. Christopher 4/24/85, Martz 3/3/88.

154 072521, "Male Reproductive Effects of Metasystox-R (MSR) After Short Term Exposure", (Microbiological Associates, Mobay study 98462, 1/27/89). Metasystox-R (oxydemeton-methyl) technical, 92%, lot 87R0010M; given by oral gavage to male Crl:CD (SD) BR rats for 5 consecutive days, at doses of 0 (water), 0.15, 0.9 or 5.0 mg/kg, 20/dose for breeding and 15 per dose for testicular evaluation by sacrifice on days 1, 7, 14, 21, 35, 56 and 112 after dosing period; no cholinesterase measurement; breeders were mated for 5 days with 1 female per male for seven mating periods; there was no apparent effect on the data from the seven matings but no positive control included for dominant lethal portion of study; in the males for testicular evaluation, body weight loss occurred during dosing at 5.0 mg/kg/day with subsequent recovery over time to control levels; percent sperm motility was reduced in the high dose group at day 1 and 7 sacrifice and in the mid- (62.5%) and high-dose (60.2%) groups at week 35 compared with controls (72.5%); in the pathology portion, the only finding noted was at day 116 at 5.0 mg/kg with 13/15 showing epithelial vacuolization in the corpus epididymis compared to 5/15 in the controls, 8/15 at 0.15 and 6/15 at 0.9 mg/kg but no significant finding in the caput or cauda epididymis; **SUPPLEMENTAL STUDY**. Gee, 3/8/89.

175 087524, "R 2170 C.N. Oxydemeton-Methyl Cytogenetic Testing of the Bone Marrow of the Chinese Hamster in vivo to Check for Chromosome Damage", (Bayer AG, FRG, 1/6/89, Mobay no. 99651). Oxydemeton-Methyl, 95.5 to 96.8% by analysis; given by oral gavage at 0 (water) or 40 mg/kg body weight, single dose; sacrificed negative and positive (cyclophosphamide) controls at 24 hours, 5/sex; sacrificed treated hamsters at 6, 24 or 48 hours, 5/sex/time; scored approximately 100 metaphases per animal; clinical signs for approximately 2 hours post dosing - apathy, tremor, cramps; dose selection based on pilot study up to 80 mg/kg; no evidence for induction of chromosomal aberrations; **NO ADVERSE EFFECT; ACCEPTABLE. Gee, 10/12/89.

192 088973 Supplement to 087524 above. Volume contains a verification requested by EPA reviewer that the slides were scored after coding. Mobay 99651-1. CDFA had already accepted the study. Gee, 5/10/91.

009 929671, Invalid IBT study. Not reviewed by Medical Toxicology.

COMMENTS: There are seventeen submissions for the chromosome mutation category, of which five (Volume 136, Record 65425; Volume 140, Records 68454 & 68455; Volume 143, Record 064891; volume 175, Record 087524) are acceptable. The unacceptable submissions

include an invalid IBT study, journal articles, and three micronucleus studies using a protocol which has been shown to be ineffective. Several of the submissions, including three acceptable studies, indicated genotoxicity. The fourth is a dominant lethal study, which is generally one of the less sensitive assays. It is also noted that the mutagenicity was found with and without activation, which is also true for the gene mutation studies. Davis, 6/88 and Gee, 10/89.

DNA DAMAGE

330-205 140414 "R 2170: Alkaline elution in vivo for the detection of induced DNA-single strand breaks in rat testes." (S. Brendler-Schwaab, Bayer AG, Department of Toxicology, Germany, #107001, 4/13/95) Male Sprague Dawley rats (Crl:CD(SD)BR) were given a single dose of R 2170 by gavage at 0 (0.5% aqueous cremophor emulsion), 5, 20 or 40 mg/kg bw and sacrificed after 4 hours. Testes cells were isolated and loaded onto polycarbonate filters at 5.1 x 10^6 per filter in triplicate, two rats per dose per trial with two trials. EMS was the positive control. Cells were lysed with SDS and protein digested with protease K. DNA was eluted at pH12.1 into 10 fractions overnight. DNA was quantitated by fluorimetry with bisbenzimide H 33258. No evidence of an increase in DNA damage as determined by the rate of elution from filters under alkaline conditions. **Unacceptable** (summary data only, no individual fraction data). Upgradeable with submission of individual data. Gee, 10/21/97.

330-205 140415 "R 2170: Alkaline elution in vitro for the detection of induced single strand breaks in CHO cells." (S. Brendler-Schwaab, Bayer AG, Department of Toxicology, # 107000, 3/16/95) CHO-WB1 cells were exposed to R 2170 (90-92%) at concentrations up to 5000 ug/ml with and without S9 activation. The induction of DNA damage was assayed by alkaline elution from polycarbonate filters at pH 12.1. Ten fractions were collected overnight and the DNA quantitated by fluorimetry using bisbenzimide H33258. The elution patterns of treated cultures were compared with the controls. Positive controls were ethyl methanesulfonate (-S9) and 2-aminoanthracene (+S9). Triplicate filters per concentration with multiple trials were included. **Possible adverse effect**:: An increase in the rate of elution was found as dose-related and reproducible. **Unacceptable (**summary data only), possibly upgradeable with submission of individual fraction data. Gee, 10/21/97.

330-205 140416 "R 2170: Alkaline elution in vitro for the detection of induced DNA-single strand breaks in rat primary testes cells" (S. Brendler-Schwaab, Bayer AG, Department of Toxicology, Germany, #107002, 3/14/95) Primary rat testes cells were treatment with R 2170 for approximately 1 hour at 0 (phosphate buffered saline), 500, 1000, 2000, 4000 or 5000 ug/ml. Treated cells were lysed on polycarbonate filters and eluted at pH 12.1 overnight in 10 fractions. DNA elution was compared with controls. Triplicate samples per concentration, two trials. No activation included. EMS as positive control was functional. Treatment with oxydemeton-methyl increased the rate of elution from the filters indicating it increased the number of single strand breaks. **Possible adverse effect. Unacceptable** (no individual data for elution patterns). Upgradeable. Gee, 10/24/97.

**140 068456, "Unscheduled DNA Synthesis in Rat Primary Hepatocytes", (Microbiological Associates, Inc., Study No. T5572.380, 3/7/88). Rat primary hepatocytes were exposed to Metasystox-R (94.6% pure, Lot No. Pt 808406113) at 0, 0.01, 0.03, 0.1, 0.3, 1.0 ul/ml for 20.5

hours; triplicate plates; duplicate assays; **ACCEPTABLE; NO ADVERSE EFFECT**. Davis 6/29/88.

089 008649, (see also 8649 under Gene Mutation): "Mutagenicity Evaluation of R 2170 in the Rec Assay and the Reverse Mutation Induction Assay", (Litton, 4/80). "R 2170," AI content unspecified, at 5000, 2500, 1000, 500, 100, 10, 0 ug/plate in Bacillis subtilis strains H17 (rec+) and M45 (rec-) ± Aroclor induced male Sprague Dawley rat S9, with EMS or DMN as positive controls; **NO ADVERSE EFFECTS; UNACCEPTABLE** and not upgradeable - test article composition not identified, single platings with no replicate test. Christopher 4/24/85.

089 008646, "Evaluation of R2170, C.N. Oxydemeton-methyl in the Primary Rat Hepatocyte Unscheduled DNA Synthesis Assay", (Litton, 11/83). Oxydemeton-methyl, AI content not identified, at 2500, 1000, 500, 250, 100, 50, 25, 10, 5, or 0 nl/ml with 2-AAF as positive control in fresh hepatocytes from F344 male (Charles River) rats; **NO ADVERSE EFFECT**, no UDS, cytotoxicity at 2500 nl/ml; originally acceptable (Christopher, 4/24/85), but **UNACCEPTABLE** in supplemental review; upgradeable with test article characterization. Martz 3/4/88.

089 008644, "Induction of Gene Conversion in Diploid Yeast by Chemicals: Correlation with Mutagenic Action and its Relevance in Genotoxicity Screening", (Bhabha Atomic Res. Ctr. (India), Mutation Research, 64:1-17, 1979). Review article comparing gene conversion in diploid yeast with other mutagenic effects in >200 chemicals; oxydemeton-methyl referenced to be **positive** in yeast assay and other unspecified test(s), referencing Fahrig, R.(1974) Comparative Mutagenicity Studies with Pesticides, IARC Sci. Pub. 10:161-181. **UNACCEPTABLE.** Christopher 4/23/85, Martz 3/8/88

089 008641, "Detection of Genetic Effect of Organophosphate Insecticides"; One-paragraph abstract in English of article in Naturwissenschaften, 60:50-51, 1973; **ADVERSE EFFECT,** mitotic gene conversion in Saccharomyces cerevisiae noted for oxydemeton-methyl, with no values or data; **UNACCEPTABLE**, abstract only. Christopher 4/22/85, Martz 3/8/88 (no new Worksheet).

COMMENTS: Although there are references in Records 008644 and 008641 to positive results in yeast gene conversion assays, there is insufficient evidence for an independent evaluation. The three studies which can be evaluated (unscheduled DNA synthesis, Records 008646 & 068456; bacterial DNA repair assay, Record 008649) are negative. It is concluded that there is no adverse effect. Davis, 6/88. Additional studies, records 140415 and 140416, indicate that there is an increase in single strand breaks when cells are exposed *in vitro*. Therefore, the conclusion is changed to a possible adverse effect. Gee, 10/97.

NEUROTOXICITY

089 008636, "Acute Delayed Neurotoxicity of METASYSTOX-R 50% Concentrate", (Mobay, 8/9/84). METASYSTOX-R, 50% oxydemeton-methyl, at 200 mg bulk/kg (median lethal dose) by oral gavage to 23 atropine and 2-PAM protected hens (White Leghorn), with another 8/group receiving TOCP (556 mg/kg), antidotes alone, or no treatment; guideline study; **NO ADVERSE EFFECT, no clinical or microscopic evidence of delayed neurotoxicity in METASYSTOX-R treated hens, positive clinical and microscopic response with TOCP. Unacceptable in prior review (Christopher, 4/25/85) because formulated product tested, not a problem in absence of effect at lethal dose. Complete and **ACCEPTABLE**. Martz 3/4/88.

152 072637, Supplement to 008636. Contains data requested by EPA reviewer on the microscopic examination of three MSR treated hens and new body weight tables for all groups. No worksheet. Gee, 3/10/89.

183 087916, "Subchronic Delayed Neurotoxicity Study with Technical Grade Oxydemeton-Methyl (METASYSTOX-R) in Hens" (Mobay Corp, 12/18/89, Mobay Report No. 99807). METASYSTOX-R (MSR) Technical, 92.6%, batch 87R0010M; 12 White Leghorn hens/dose administered MSR in deionized water by oral gavage at 0, 1, 5, and 10 mg/kg/day 5 days/week for 13 weeks; additional 12 hens administered TOCP in corn oil at 10 mg/kg/day; whole blood cholinesterase levels were significantly reduced in the mid- and high-dose groups; **NO ADVERSE EFFECTS - no clinical or microscopic evidence of delayed neurotoxicity in MSR treated animals; systemic NOEL $\geq$ 10 mg/kg/day; cholinesterase NOEL = 1 mg/kg/day. **ACCEPTABLE.** (C. Lewis, 4/13/90; G. Patterson, 4/13/90)

034 929689, Harris Labs, 12/29/64; Undefined test material at 0, 50, 100, and 200 ppm for 30 days in feed to groups of 6 Leghorn hens, followed by: 1) sacrifice for histopathology of 3 per group and 2) 30 days observation and sacrifice for the remaining 3 per group; **INSUFFICIENT INFORMATION FOR ASSESSMENT; UNACCEPTABLE:** no positive control, no dose justification, questionable route of administration, insufficient test material characterization. Christopher 4/30/85.

SPECIAL STUDIES

133 060989 "Fourteen-Day Cholinesterase Activity Study of Oxydemeton-Methyl Technical (METASYSTOX-R) with Rats by Dermal Application", (Mobay (KS), 12/21/87 #94978). Oxydemeton-methyl, 94.6% pure, by dermal application at 5.0, 1.0, 0.3, or 0 mg/kg/day to 5/sex/level Sprague-Dawley descendents for 14 days; cholinesterase inhibition (CHEI) at 5.0 mg/kg 48 and 60% in brain, 37%-46% in RBC and 30-50% in plasma; at 1.0 mg/kg, CHEI was 12 and 16% in the brain; at 0.3 mg/kg, CHEI was 11% in brain of females. No body weight changes, clinical signs, or gross necropsy findings were associated with CHEI. Martz 1/28/88; Gee 8/30/95.

123 057657, "MSR Progress Report - Cholinesterase Activity of MSR in Rats after Dermal, Oral Gavage and Dietary Administration Over a Two-week Period"; Mobay, 5/22/87; 3 page progress report; complete report in Volume 133. Martz, 3/4/88.

133 064855, "Fourteen-Day Cholinesterase Activity Study of Oxydemeton-Methyl (METASYSTOX-R 50% Concentrate) in Ration with Rats", (Mobay (KS), 12/21/87). Metasystox-R 50% Concentrate, 54.8% oxydemeton-methyl, in the feed at 50, 9, 3, or 0 ppm AI to 5/sex/level Sprague-Dawley descendents for 14 days; CHE inhibition at 50 ppm 80% brain, 50% RBC, 75% plasma, lesser at lower dose levels, NOEL < 3 ppm; no clinical signs of CHE inhibition; slight reduction of body weight gain in 50 ppm males. Martz, 1/28/88.

133 064856, "Fourteen-Day Cholinesterase Activity Study of Oxydemeton-Methyl Technical (METASYSTOX-R) with Rats by Oral Gavage", (Mobay (KS), 12/21/87). Oxydemeton-methyl, 94.6% pure, by gavage at 2.5, 0.45, 0.15, or 0 mg/kg/day to 5/sex/level Sprague-Dawley descendents for 14 days; cholinesterase inhibition (CHEI) at 2.5 mg/kg 67% in brain, 45%-60% in RBC and plasma; at 0.45 mg/kg, CHEI was 25% in all 3 areas; at 0.15 mg/kg, CHEI was 11% in brain and 0-16% in RBC's and plasma. No body weight changes, clinical signs, or gross necropsy findings were associated with CHEI. Martz, 1/28/88.

COMMENT: A number of additional cholinesterase inhibition studies have been submitted. Davis, 1988.